

**United States Patent Application**

**AUTOMATED PRECISION OBJECT HOLDER AND  
METHOD OF USING SAME**

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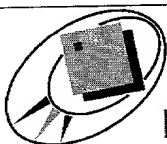
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## **AUTOMATED PRECISION OBJECT HOLDER AND METHOD OF USING SAME**

### **CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application is a continuation-in-part of International Application No. PCT/US01/19274, filed June 15, 2001, which is a continuation-in-part of US Appl. No. 09/596,752, filed June 15, 2000, which applications are incorporated herein by reference for all purposes.

### **BACKGROUND OF THE INVENTION**

#### **Field of the Invention**

[0002] This invention pertains to the field of automated mechanical systems. More specifically, the present invention relates to an automated system for precisely positioning an object for further automated processing.

#### **Background**

[0003] Many industrial fields require the precise positioning of an object for automated processing. The success of the human genome project, for example, is due in part to a transition from traditional laboratory bench top processes to more automated high-throughput systems. The studies in genomics and proteomics that are required to interpret the data obtained from the human genome project will likewise require improved high-throughput systems. High-throughput systems are also used for synthesis of large numbers of compounds and the subsequent screening of such libraries of compounds.

[0004] To increase throughput, these automated systems for chemical synthesis and for screens and assays typically employ a microtiter (or specimen) plate. The microtiter plates can be used, for example, to hold multiple compounds and materials, to conduct multiple assays on one or more compounds, to facilitate high throughput screening and to accelerate the production and testing of a large number of samples. Each microtiter plate typically has many individual sample wells, for example hundreds or even more than a thousand wells. Each of the wells forms a container into which a sample or reagent is placed.

Since an assay or synthesis can be conducted in each sample well, hundreds or thousands of tests can be performed using a single plate. Microtiter plates are configured to meet industry standards. For example, some commonly used standard plates have 96, 384, or 1,536 wells. Such plates are available from, for example, Greiner America Corp., P.O. Box 953279, Lake Mary, Florida 32795-3279. The plates generally can be heated, cooled, or shaken to facilitate a desired process.

[0005] Coupling the use of microtiter plates with automated processing systems enable the synthesis and/or testing of hundreds of thousands of samples in a single day. Automated equipment, such as automated liquid dispensers, can receive appropriately configured microtiter plates and deposit samples or reagents into the plate wells. Other known automated equipment facilitates the processing and testing of samples using loaded microtiter plates.

[0006] In order to perform a high throughput assay with a high degree of reliability and repeatability, the high throughput system needs to accurately, quickly, and reliably position individual microtiter plates for processing. For example, microtiter plates must be placed precisely under liquid dispensers to enable the liquid dispenser to deposit samples or reagents into the correct sample wells. A positioning error of only a few thousandths of an inch can result in a sample or reagent being dispensed into a wrong sample well. Such a mistake can not only lead to a failed test, but such a mistake can lead to incorrect test results which others may rely upon for critical decision making, such as a medical treatment path for a patient. Further, even a minor positioning error may cause a needle or tip of the liquid dispenser to crash into a wall or other surface, thereby damaging the liquid dispenser.

[0007] Current, conventional automated positioning devices are not known to operate with sufficient positioning accuracy to reliably and repeatably position a high-density microtiter plate for automated processing. For example, typical conventional robotic systems generally achieve a positioning tolerance of about 1 mm. Although such a tolerance is adequate for some low density microtiter plates, such a tolerance is unacceptable for high density plates, such as a plate with 1536 wells. Indeed, a positioning error of one mm for a 1536 well microtiter plate could cause a sample or reagent to be deposited entirely in the wrong well, or cause damage to the system, such as to needles or tips of the liquid dispenser.

[0008] Due to the imprecision in placement of microtiter plates using conventional known systems, additional precautions are generally taken to avoid undesirable

test results. For example, tests or screens may be conducted using manual intervention to assure plates are properly positioned prior to performing a high precision task, such as dispensing sample or reagent into sample wells. Such manual intervention, however, dramatically slows the automated process and is not highly repeatable due to the normal inaccuracies and uncertainties relating to human handling.

[0009] Alternatively, tests or screens may be performed using lower density microtiter plates with fewer sample wells. In that regard, the physical size of the well is larger so the conventional automated system is more likely to process the correct well. For example, a test can be performed using a plate with only 96 wells, rather than a more dense 1536 wells. By having fewer sample wells the need for accuracy is decreased, and the repeatability and reliability of the test may be improved. However, by using microtiter plates with fewer sample wells, the overall throughput from an automated system dramatically falls. The cost of each assay is increased dramatically, as the larger wells of the lower-density plates require larger volumes of reagents. Such an inefficient use of system resources is not only costly from a financial standpoint, but may result in the delayed discovery of important biotechnology or medical therapies.

[00010] In another effort to assure reliability in conventional systems, several sample wells in a microtiter plate may be identified as control wells. These control wells are strategically positioned such that if a step of the automated process is completed while the plate is mispositioned, the control well receives a particular known sample or reagent. At a later time in the process, the control wells are tested to determine if the particular known sample or reagent was introduced into the control well. If so, the microtiter plate will be identified as having been mishandled and may be appropriately disregarded. For example, a microtiter plate having a control well that fails quality assurance will be removed from the high throughput screening system and all test results from that microtiter plate ignored. Although such a system offers some assurance of the reliability of a test, throughput for the entire system is reduced by the number of cells required as control cells. Further, the system does not recognize positioning errors until later in the processing cycle, which wastes valuable system resource for continued processing of a mishandled plate.

[00011] Robotics and automated processing systems are also used in other industries. Often, such systems require that an object be precisely positioned and retained in that position. For example, a robotic system for machining a part to close tolerances requires that the part be held in a precise location relative to the machining devices.

[00012] Therefore, a need exists for an object holder that can accurately, reliably, and quickly position an object for further processing in an automated system. The present invention fulfills these and other needs.

### SUMMARY OF THE INVENTION

[00013] The present invention provides positioning devices for precisely positioning a microtiter plate on a support. The positioning devices have at least a first alignment member that is positioned to contact an inner wall of the microtiter plate when the microtiter plate is in a desired position on the support. An inner wall 88 of a microtiter plate is shown in, for example, Figure 4. In some embodiments, two or more alignment members are positioned to contact a single inner wall of the microtiter plate when the microtiter plate is in the desired position on the support. The use of an inner wall of the microtiter plate as an alignment surface greatly increases the precision with which the microtiter plate is positioned on the support compared to, for example, aligning the microtiter plate using an outer wall, thereby facilitating further processing of the samples contained in the microtiter plate. The positioning devices can further include at least a second alignment member that is positioned to contact a second wall of the microtiter plate when the microtiter plate is in the desired position on the support. This second wall is preferably an inner wall of the microtiter plate.

[00014] The invention also provides a retaining device for retaining a microtiter plate in a desired position on a support. The retaining devices include a vacuum plate which, when a vacuum is applied, holds the microtiter plate in the desired position. The vacuum plate, in some embodiments, has an interior surface and a lip surface, with the interior surface being recessed relative to the lip surface.

[00015] Also provided by the invention is an object holder for precisely positioning an object on a support. The object holders include: a) a first pusher for moving the object in a first direction so that a first alignment surface of the object contacts a first set of one or more alignment members; and b) a second pusher for moving the object in a second direction so that a second alignment surface of the object contacts a second set of one or more alignment members. In presently preferred embodiments, either or both of the pushers includes a lever pivoting about a pivot point. The lever can be operably attached to a spring or equivalent, which causes the pusher to apply a constant force to the object to, for example, move the object in the first direction against the first set of alignment members.

[00016] The object holders of the invention can also include a controller that first directs the first pusher to move the object in a first direction, then directs the second pusher to move the object in a second direction, and (optionally) subsequently directs a retaining device to be activated.

[00017] Also provided by the invention are automated processing systems that include one or more of the object holders, positioning devices, and retaining devices described herein. These automated processing systems are useful, for example, for performing high-throughput assays or reactions in microtiter plates, among other things. The automated processing systems can include a robotic device for placing a microtiter plate on the object holders. Liquid dispensers that can deposit reagents in wells of the microtiter plates also are often included in the automated processing systems.

[00018] The invention also provides object holders that are constructed to precisely retain an object in a desired orientation. To facilitate precise and efficient positioning, the object holder has a retaining device on a support fixture for receiving the object. First and second alignment members are supported on the fixture for cooperating with respective alignment surfaces on the object. The object is generally positioned relative the alignment members. A first pusher is arranged to move one alignment surface of the object against the first alignment member, and a second pusher is arranged to move the other alignment surface of the object against the second alignment member, thereby moving the object precisely into a desired orientation. With the object precisely in the desired orientation, a controller activates the retaining device to retain the object in the object holder in the desired orientation. In use, the object is generally positioned on the fixture relative to the alignment surfaces. The first pusher and the second pusher move the object into the desired orientation, and the retaining device is activated.

[00019] The object holders are, in some embodiments, adapted to position and retain microtiter plates. Both the first and second alignment surfaces are generally wall surfaces of the plate. Microtiter plates are generally substantially rectangular, with an x-axis and a y-axis (FIGS 3-5). Thus, the first alignment surface can be a y-axis wall, and the first pusher cooperates with another y-axis wall. The second alignment surface can then be an x-axis wall, and the second pusher cooperates with another x-axis wall. Microtiter plates also generally have an inner wall 88 and an outer wall 85, the outer wall generally defining the peripheral shape of the plate, and the inner wall generally defining a well area 92 on the plate. In presently preferred embodiments, both the first and second alignment members are

received in an area 94 between the outer wall and an inner wall. The object holders can include retention device that includes a vacuum plate that cooperates with a bottom of the well area 92 to securely hold the plate.

[00020] Advantageously, the object may be generally positioned relative the alignment surfaces using a positioning device having a relatively large positioning tolerance. For example, the object may be positioned using a robotic device with about one mm tolerance, and then the object holder can more precisely orient the object. Accordingly, the object holder may be used in conjunction with known, conventional positioning devices to more precisely position objects.

[00021] Also provided by the invention are methods of receiving and retaining an object in a desired orientation. The objects have a first alignment surface and a second alignment surface, and the methods involve: a) placing the first alignment surface of the object loosely adjacent a first alignment member, and placing the second alignment surface of the object loosely adjacent a second alignment member; b) moving a first pusher against the object so that the first alignment surface is held firmly against the first alignment member; c) moving a second pusher against the object so that the second alignment surface is held firmly against the second alignment member; and d) clamping, responsive to verifying the first and second pusher are properly tensioned, the object securely to a fixture.

[00022] Software programs for directing a computer to carry out these and related methods for precisely positioning objects are also provided. For example, the invention provides a software program that operates on a controller to implement a method that has the following steps: a) receiving a signal that a microtiter plate has been generally positioned on a vacuum plate; b) activating a first pusher to move the microtiter plate into contact with a first alignment member; and c) activating a second pusher to move the microtiter plate into contact with a second alignment member. The steps involved in positioning the object can involve, for example, a) generating a y-axis signal; b) transmitting the y-axis signal to a y-axis piston to cause the y-axis piston to move a y-axis pusher lever into contact with the object to move the object against a y-axis alignment member; c) receiving a signal that the y-axis pusher lever is properly positioned; d) generating an x-axis signal; e) transmitting the x-axis signal to an x-axis piston to cause the x-axis piston to move an x-axis pusher into contact with the object to move the object against an x-axis alignment member; f) receiving a signal that the x-axis pusher is properly positioned; g) generating a vacuum signal to activate a vacuum source that clamps the object firmly against the vacuum

plate; h) generating a ready signal that indicates the object is precisely positioned; and i) transmitting the ready signal to another processing device.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

[00023] FIG. 1 is a perspective view of an object holder made in accordance with the present invention.

[00024] FIG. 2 is a top view of an object holder made in accordance with the present invention.

[00025] FIG. 3 is a top view of a microtiter plate.

[00026] FIG. 4 is a bottom view of the microtiter plate shown in FIG. 3.

[00027] FIG. 5 is a cross-sectional view of the microtiter plate shown in FIG. 3.

[00028] FIG. 6 is a diagrammatic representation of an x-axis pusher and a y-axis pusher positioning a microtiter plate.

[00029] FIG. 7 is a block diagram showing electrical, vacuum, and air interconnections in an object holder made in accordance with the present invention.

[00030] FIG. 8 is a partial cross-sectional view of a y axis pusher lever made in accordance with the present invention.

[00031] FIG. 9 is a partial exploded view of the piston and lever mechanism for a y axis pusher made in accordance with the present invention.

[00032] FIG. 10 is prospective view of a y axis pusher lever made in accordance with the present invention.

[00033] FIG. 11 is a diagram showing part placement on the underside of an object holder made in accordance with the present invention.

[00034] FIG. 12 is a flowchart showing a method of precisely positioning an object according to the present invention.

[00035] FIG. 13 is a method of removing a plate from an object holder in accordance with the present invention.

### **DETAILED DESCRIPTION**

[00036] The invention provides devices for precisely positioning objects on a support, and for retaining objects in a desired position on a support. The devices are often used in conjunction with automated systems, such as robotic systems, that require precise placement of an object that is to be subjected to further processing. For example, robotic systems used in biotechnology often use microtiter plates as containers for samples and



reagents. The microtiter plates must be precisely positioned on the appropriate support in order for the other components of the system to properly interact with the samples contained in the microtiter plate wells. Similarly, a device of the invention is useful for positioning block material for highly precise milling work.

### **Positioning Devices**

[00037] The invention provides positioning devices for precisely positioning an object on a support. Once an object is generally positioned near a desired position, the positioning devices move the object to the precise desired position. Accordingly, the object holders of the invention can be used in conjunction with known, conventional positioning devices to more precisely position objects. For example, conventional automated devices, such as known robotic positioning devices, can place an object on a support. Such previously known robotic devices are generally capable of moving and positioning an object such as a microtiter plate within about a one mm tolerance. In that regard, the known robotic systems can generally position the microtiter plate on a support, but are not capable of achieving the precision required for positioning high density microtiter plates. A positioning error of one mm for a high-density (e.g., 1536 well or greater) microtiter plate could cause a sample or reagent to be deposited entirely in the wrong well, or cause damage to the system, such as to needles or tips of the liquid dispenser.

[00038] The object holders of the invention generally include one or more alignment members against which a surface of an object is in contact when the object is in a desired position on the object holder. The alignment members are arranged such that when an object such as a microtiter plate is initially positioned near the alignment members, the object is generally positioned for further processing. Such general positioning may be accomplished with conventional, known robotic systems. For example, the general positioning may place the object within one mm of its desired orientation. However, such a general positioning of the microtiter plate or other object is insufficiently precise for high throughput processing. After the object is generally positioned, the object holder of the invention is activated to more precisely position the object for further processing.

[00039] For precise positioning along two different axes, the object holders of the invention generally have one or more alignment members along each of the two axes of the object. For example, Figures 1 and 2 show one embodiment of an automated object holder **10** in accordance with the present invention. Object holder **10** generally comprises a

fixture **15** supporting a retaining device **20**. The protrusions **25** and **30** function as alignment members. The illustrated embodiment of the object holder **10** has two y-axis protrusions **30** and an x-axis protrusion **25** supported from the fixture **15**. Accordingly, the y-axis protrusions **30** and x-axis protrusion **25** are fixedly positioned relative to the vacuum plate **20**, which, in this embodiment, acts to hold the object in position once it has been precisely positioned. The y-axis locating protrusions **30** are constructed to cooperate with a y-axis surface of an object (e.g., an y-axis wall of a microtiter plate), while the x-axis protrusion **25** is constructed to cooperate with an x-axis surface of the object (e.g., an x-axis wall of a microtiter plate).

[00040] The alignment members can be, for example, locating pins, tabs, ridges, recesses, or a wall surface, and the like. In presently preferred embodiments, the alignment members have a curved surface that is in contact with a properly positioned object. The use of a curved surface minimizes the effect of, for example, roughness of the object surface that contacts the alignment member. The use of two alignment members along one axis and one alignment member along the second axis, as shown in Figures 1 and 2, is another approach to minimize the effect of surface irregularities on the proper positioning of the object. The object is in contact with three points along the object surface, so proper alignment is not dependent upon the entire object surface being regular.

[00041] Another aspect of the invention applies specifically to positioning of microtiter plates. A microtiter plate **82** is shown in Figures 3, 4, and 5. The microtiter plate **82** generally comprises a well area **90** which has many individual sample wells for holding samples and reagents. Microtiter plates are available in a wide variety of sample well configurations, including commonly available plates with 96, 384, and 1536 wells. It will be appreciated that microtiter plates are available from a variety of manufacturers in a variety of configurations. The microtiter plate **82** has an outer wall **84** having a registration edge **86** at its bottom. The microtiter plate **82** has a bottom surface **92** below the well area on the plate's bottom side. The bottom surface **92** is separated from the outer wall **84** by a space **94**. The space **94** is bounded by a surface of the outer wall **84** and by an inner wall **88** at the edge of the bottom surface **92**. Although there may be some lateral supports **93** in the space **94**, the space **94** is generally open between the inner wall **88** and an inner surface of the outer wall **84**.

[00042] According to the invention, to precisely position a microtiter plate the alignment members of the object holder preferably are arranged to cooperate with an inner

wall 88 of the microtiter plate. The inner wall 88 is advantageously used, as the inner wall is typically more accurately formed and is more closely associated with the perimeter of the sample well area, as compared to an outer wall of the plate 82, such as wall 84. Accordingly, aligning the microtiter plate relative an inner wall, such as inner wall 88, is generally preferred to aligning with an outer wall, such as wall 84. The increased positioning precision that is obtained by using an inner wall as the alignment surface makes possible the use of high-density microtiter plates, such as 1536 well plates. As shown in Table 1, the use of an inner well for positioning of polypropylene (A) and polystyrene (B) 1536-well plates results in much more precise positioning of the plate compared to the precision obtained using a spring clip fixture (C) such as was previously known in the art.

**Table 1**

**A. PolyPro 1536 Plate (in positioning fixture)**

Well Position	Axis	Plate 1	Plate 2	Plate 3	Plate 4	Plate 5	Range	Ave
A 1	X	-0.342	-0.337	-0.337	-0.334	-0.331	0.011	-0.3362
	Y	-107.195	-107.198	-107.206	-107.200	-107.203	0.011	-107.2004
A 48	X	-0.106	-0.108	-0.104	-0.103	-0.105	0.005	-0.1052
	Y	-2.640	-2.638	-2.628	-2.628	-2.631	0.012	-2.6330
FF 48	X	68.893	68.892	68.903	68.903	68.905	0.013	68.8992
	Y	-2.748	-2.750	-2.742	-2.739	-2.735	0.015	-2.7428
FF 1	X	68.661	68.664	68.677	68.674	68.679	0.018	68.6710
	Y	-107.387	-107.385	-107.389	-107.390	-107.387	0.005	-107.3876
P 18	X	33.134	33.134	33.145	33.142	33.142	0.011	33.1394
	Y	-69.455	-69.456	-69.450	-69.456	-69.457	0.007	-69.4548
P 32	X	33.203	33.202	33.211	33.209	33.209	0.009	33.2068
	Y	-38.290	-38.295	-38.294	-38.294	-38.293	0.005	-38.2932
Ave range (mm)							0.010	

	Actual	Theor
Distance Between A1 and A48	104.5674	105.75
Distance Between FF1 and FF48	104.6448	105.75
Distance Between A1 and FF1	69.0072	69.75
Distance Between A48 and FF48	69.0044	69.75

**B. PolyStyrene 1536 Plate (in positioning fixture)**

Well Position	Axis	Plate 1	Plate 2	Plate 3	Plate 4	Plate 5	Range	Ave
A 1	X	-0.361	-0.361	-0.362	-0.362	-0.362	0.001	-0.3616
	Y	-107.239	-107.245	-107.245	-107.244	-107.243	0.006	-107.2432
A 48	X	-0.106	-0.112	-0.116	-0.109	-0.107	0.010	-0.1100
	Y	-1.597	-1.607	-1.611	-1.603	-1.602	0.014	-1.6040
FF 48	X	69.612	69.609	69.602	69.611	69.613	0.011	69.6094
	Y	-1.694	-1.703	-1.699	-1.697	-1.700	0.009	-1.6986
FF 1	X	69.357	69.357	69.356	69.356	69.356	0.001	69.3564
	Y	-107.475	-107.479	-107.474	-107.477	-107.478	0.005	-107.4766
P 18	X	33.478	33.476	33.475	33.477	33.480	0.005	33.4772
	Y	-69.121	-69.129	-69.130	-69.125	-69.126	0.009	-69.1262
P 32	X	33.553	33.549	33.545	33.552	33.553	0.008	33.5504
	Y	-37.632	-37.639	-37.635	-37.636	-37.635	0.007	-37.6354

**Ave range (mm) 0.007**

	Actual	Theor
Distance Between A1 and A48	105.6392	105.75
Distance Between FF1 and FF48	105.7780	105.75
Distance Between A1 and FF1	69.7180	69.75
Distance Between A48 and FF48	69.7194	69.75

**C. PolyStyrene 1536 Plate (in spring clip fixture)**

Well Position	Axis	Plate 1	Plate 2	Plate 3	Plate 4	Plate 5	Range	Ave
A 1	X	117.089	117.093	117.070	117.085	117.097	0.027	117.0868
	Y	-123.704	-123.747	-123.746	-123.755	-123.742	0.051	-123.739
A 48	X	117.019	117.041	117.060	117.032	117.029	0.041	117.0362
	Y	-18.058	-18.093	-18.090	-18.100	-18.086	0.042	-18.0854
FF 48	X	186.739	186.759	186.780	186.752	186.750	0.041	186.756
	Y	-17.949	-17.991	-18.015	-18.002	-17.976	0.066	-17.9866
FF 1	X	-186.810	-186.813	-186.792	-186.803	-186.819	0.027	-186.807
	Y	-123.730	-123.783	-123.807	-123.795	-123.766	0.077	-123.776
P 18	X	150.816	150.825	150.819	150.814	150.824	0.011	150.8196
	Y	-85.481	-85.528	-85.537	-85.538	-85.515	0.057	-85.5198
P 32	X	150.792	150.807	150.813	150.798	150.802	0.021	150.8024
	Y	-53.989	-54.038	-54.046	-54.046	-54.023	0.057	-54.0284

**Ave range (mm) 0.043**

**[00043]** These results demonstrate that the use of the inner wall of the microtiter plate as an alignment surface results in much more precise and reproducible positioning of the microtiter plate on a support than use of an outer wall of the microtiter plate.

**[00044]** Further, by having the alignment members (e.g., alignment protrusions **25** and **30**) cooperate with an inner wall **88** of the plate **82**, minimal structures are needed adjacent the outside of the plate. In such a manner, a robotic arm or other transport is able to readily access the plate **82**. Having the protrusions positioned adjacent the inner wall **88** thereby facilitates more easily transporting the plate **82**. However, it will be appreciated that the protrusions can be placed in alternative positions and still facilitate the precise positioning of the plate.

**[00045]** The object holders of the invention generally include one or more movable members. The movable members function to move an object against one or more alignment members. For example, once an object is placed in the general location of the alignment member(s), the movable members (termed "pushers" herein) move the object so that an alignment surface of the object is in contact with one or more of the alignment members of the object holder. The object holder can have pushers for positioning of the object along one or more axes. For example, an object holder will often have one or more pushers that position an object along an x-axis, and one or more additional pushers that position the object along a y-axis. The pushers can be moved by means known to those of skill in the art. For example, springs, pistons, elastic members, electromagnets or other magnets, gear drives, and the like, or combinations thereof, are suitable for moving the pushers so as to move the object into a desired position.

**[00046]** One embodiment of an object holder having pushers for positioning a microtiter plate along both the x-axis and the y-axis is shown in Figures 1 and 2. When the microtiter plate is generally positioned adjacent the x and y-axis protrusions, the bottom surface of the microtiter plate is directly above the top surface **22** of the vacuum plate **20**. A y-axis pusher **35**, which extends through a slot **40** in the fixture **15**, is used to apply pressure to a y-axis side wall of the microtiter plate. Sufficient force is applied to the plate at the plate contact **45** to push the microtiter plate against the y-axis protrusions **30**. When the microtiter plate is pushed against the y-axis protrusions **30**, an x-axis pusher **50**, which extends through slot **55** of the fixture, is used to push an x-axis wall of the microtiter plate towards the x-axis protrusion **25**. In such a manner, the microtiter plate is accurately and precisely positioned relative both the x-axis and y-axis protrusions. It is sometimes advantageous, although not

necessary, to have one or more of the pushers contact an inner wall of a microtiter plate rather than an outer wall. With this arrangement, the alignment members and pushers are underneath the microtiter plate. This leaves the area surrounding the exterior of the plate free of protrusions that could otherwise interfere with other devices that, for example, place the microtiter plate on the support.

[00047] The object holder embodiment shown in Figures 1 and 2 has a vacuum plate that functions as a retaining device to hold a properly positioned object in the desired position. With both the y-axis pusher **35** and the x-axis pusher **50** applying sufficient force to precisely place the microtiter plate, a vacuum source (not shown) applies a vacuum through vacuum line **65** into vacuum holes **60**.

[00048] Referring now to FIG. 6A-D, one embodiment of a general progression of positioning an object in the object holder **10** is described. It is recognized that the object holder can employ means that are equivalent to those illustrated to move an object into a desired position on the surface. Similarly, although the figures demonstrate the positioning of a microtiter plate in particular, one can readily adapt the arrangement of the object holder components to position objects other than microtiter plates. FIG. 6 shows a simplified bottom view of a microtiter plate **82** resting on the vacuum plate (not shown). FIG. 6A shows a loading position where the microtiter plate **82** is generally positioned relative the x-axis and y-axis protrusions **25** and **30**. When generally positioned, the microtiter plate **82** is positioned such that the y-axis protrusions **30** are received into the opening **94** along the y-axis edge of the microtiter plate and the x-axis protrusion **25** is received into the space **94** along the x-axis edge of the microtiter plate. Accordingly, in this presently preferred embodiment the protrusions are positioned in the space **94** between the inner wall **88** and the outer wall **84**. It will be appreciated that the protrusions may cooperate with the microtiter plate in alternative configurations to place the microtiter plate in a generally positioned orientation. Further, to facilitate loading, both the y-axis pusher **35** and the x-axis pusher **50** are positioned away from the microtiter plate **82**.

[00049] Referring now to FIG. 6B, the y-axis pusher **35** is moved so as to contact an outer y-axis edge of the microtiter plate **82**. As described above, the pusher could also be arranged to contact an inner well surface of the microtiter plate. The y-axis pusher **35** is moved with sufficient force to firmly force the plate contact **45** against a wall **84** of the microtiter plate **82**. As the y-axis pusher **35** is pressed against the microtiter plate **82**, the microtiter plate is moved, if necessary, to firmly position the inner wall **88** against the y-axis

protrusions 30. As the y-axis pusher 35 generally contacts the y-axis edge of the microtiter plate in a central location, the microtiter plate is moved with a minimum skewing force. In such a manner the microtiter plate is firmly and reliably positioned in the y-axis.

[00050] With the microtiter plate 82 firmly positioned in the y-axis, FIG. 6C shows that the x-axis pusher 50 is moved against an x-axis wall of the microtiter plate 82. In such a manner the x-axis pusher 50 moves the microtiter plate 82 to position the inner wall 88 against the x-axis protrusion 25. While the x-axis pusher 50 is moving and holding the plate against the x-axis alignment member, the y-axis pusher 35 remains firmly pressed against the y-axis wall of the microtiter plate 82. To facilitate the microtiter plate 82 moving in the x direction relative the contact 45, the contact 45 is preferably constructed to be a low friction element. For example, the low friction contact point 45 can be mounted on a spring-loaded member, which can keep a constant force against the microtiter plate 82 while enabling the microtiter plate to be moved in the x-axis by the x-axis pusher 50. Figure 10 shows an example of a suitable spring-loaded member. The contact point can also be coated with a low-friction material, such as TEFLON™, and the like. A low friction contact point can also be constructed by using a rolling contact point, for example, or other means to reduce friction. A DELRIN™ ball plunger is another example of a suitable low friction contact point.

[00051] As shown in Fig. 6D, when the microtiter plate 82 has moved into position by the x-axis pusher 50, the microtiter plate is precisely positioned for further processing. With the plate precisely positioned, a vacuum source (not shown) is activated, thereby securely drawing the microtiter plate 82 against a vacuum plate. Accordingly, the microtiter plate 82 is securely retained in its precise position, thereby allowing accurate and reliable further processing.

### Retaining Devices

[00052] The invention also provides retaining devices for retaining an object, such as a microtiter plate, in a desired position on the support. These retaining devices of the invention include a vacuum plate upon which the object is placed. The vacuum plate generally has a top surface upon which the object to be retained is placed. One or more openings are present through which air can be withdrawn from the space between the top surface of the vacuum plate and the bottom surface of the object. The opening or openings can be connected to a vacuum source. When the object is properly positioned on the support

and a vacuum is applied, an airtight seal is formed between the object and the vacuum plate, thus holding the object in the desired position. For example, if the object is a microtiter plate, the bottom surface of the microtiter plate forms a seal with the top surface of the vacuum plate.

[00053] An example of a retaining device of the invention is shown in Figures 1, 2 and 8. In this embodiment, the vacuum plate **20** has a top surface **22** which generally comprises a central interior area **69** and a lip area **67** which are separated by the vacuum groove **63**. When the object is generally positioned in the desired position, a bottom surface of the object rests on the lip area **67** of the top surface **22**. A vacuum source (not shown) applies a vacuum through vacuum line **65** into vacuum holes **60**. The vacuum holes **60** are in communication with a vacuum groove **63** which generally is positioned inside the perimeter of the vacuum plate **20**. In such a manner, the vacuum effect is transferred around the entire perimeter of the plate. As the vacuum effect draws the bottom surface of the object towards the top surface **22** of the vacuum plate **20**, the object is retained by the vacuum force to the vacuum lip **67** and the interior vacuum plate **69**.

[00054] In the example illustrated in Figures 1, 2 and 8, the retaining device **20** is provided as a rectangular vacuum plate, with a y-axis length constructed longer than an x-axis length. This particular vacuum plate **20** is sized and constructed to cooperate with a bottom surface of a microtiter plate to retain the microtiter plate securely against a top surface **22** of the vacuum plate **20** when a vacuum source is activated. The vacuum plate also can be configured to retain objects other than microtiter plates. For example, the vacuum plate can be shaped to form a suction with any flat surface of an object. A rectangular slot, for example, can be used to retain an object having a flat rectangular surface.

[00055] Figure 11 shows one embodiment of the retaining device of the invention. A vacuum source (not shown) connects to vacuum line **230** which connects to vacuum inlets **240** and **235**. The vacuum line inlets **235** and **240** are directly connected into vacuum holes which extend through the vacuum plate and communicate with the vacuum groove. In a presently preferred embodiment, the vacuum holes are positioned adjacent the perimeter of the vacuum plate and use a vacuum groove to communicate the vacuum around the perimeter of the vacuum plate. It will be appreciated that other positioning of the vacuum holes and other arrangements can be used to improve the vacuum sealing capability of the vacuum plate.



[00056] Objects sometimes have lower surface imperfections that can interfere with the formation of an airtight seal between the vacuum plate and the object surface. Such imperfections can include, for example, warping, height variations, and other structural imperfections. For example, the bottom surface of a microtiter plate may bow slightly so that the center portion of the microtiter plate extends below the perimeter edge of the microtiter plate. Accordingly, if such a bowed plate is placed on the vacuum plate 20, the bowed portion of the microtiter plate can contact the interior plate area 69 and not allow a perimeter edge of the plate to fully engage the lip area 67. In such a manner, when vacuum is applied to the vacuum channel 63, a gap sufficient to avoid vacuum sealing may remain between the perimeter edge of the microtiter plate and the lip area 67. With such a gap, it may not be possible to vacuum seal the microtiter plate to the vacuum plate.

[00057] To accommodate such imperfections in microtiter plates and other objects, the interior vacuum surface 69 may be recessed slightly below the vacuum lip 67. By recessing the interior surface 69 slightly, the probability that the perimeter edge of the microtiter plate will fully contact the lip area 67 is increased. The depth and other dimensions of the recess will depend upon the expected variations in the bottom surface of the objects. Typically, the depth of the recess is between about 0.001 and 0.01 inches. For microtiter plates, the interior vacuum area is preferably positioned about 0.002 inches below the top surface of the lip 67 because it has been found that the 0.002-inch variation in height is not sufficient to disrupt the sample wells when the microtiter plate is sealed to the vacuum plate 20. Another approach by which to avoid distortion of the object, the recessed area can be partially or completely filled with a porous matrix material or other support members (e.g., ribs) that provide support for the bottom surface of the object while still allowing formation of a vacuum seal. The use of a support allows the use of a recess of greater depth, if desired.

[00058] The retaining devices of the invention can also include sensing switches or other means for sensing whether a vacuum effect is present between an object and the vacuum plate. For example, Figure 2 shows a vacuum switch hole 80, which in this particular embodiment is positioned at the base of the vacuum groove 63. The vacuum switch hole communicates the vacuum level to a vacuum sensing switch, which confirms a sufficient level of vacuum beneath the object. In such a manner, the vacuum force retaining the object can be measured and monitored while the object is retained against the vacuum plate 20. If the vacuum level is insufficient, the sensing switch can send a signal to a

controller, or to a human operator, that the object is not properly positioned and/or retained and thus is not ready for further processing. Conversely, if a vacuum is sensed, the switch can signal the controller to proceed with further processing.

[00059] An example of a retaining device that includes a sensing device is shown in Figure 11, which generally shows a bottom side of a fixture **15** with the vacuum plate **20** positioned on the top surface of the fixture **15**. Although from the bottom view in FIG. 11 the vacuum plate is not visible, dotted line **21** shows the general positioning of the vacuum plate **20** on the other side of the fixture **15**. As shown, a vacuum switch hole is positioned in the vacuum groove. The vacuum switch hole communicates with vacuum switch inlet **265**, which connects to vacuum switch **275** through vacuum switch line **270**. The vacuum switch **275** electrically connects to a controller **105** through control line **280** for communicating status of vacuum to the controller. In that regard, the controller **105** receives a signal when sufficient vacuum is achieved at the vacuum plate to draw the microtiter plate firmly against the vacuum plate. The controller **105** can also communicate to the vacuum source via control line **225** and optionally to a air supply source (described below) via control line **220**. The controller **105** can also receive direction and send status information to other system components via system connection line **285**.

[00060] Once the vacuum source has securely retained the microtiter plate or other object against the vacuum plate **20**, additional processes may be performed reliably and accurately to the microtiter plate. When processing of the microtiter plate or other object is completed, the vacuum source is deactivated, thereby releasing the object from the vacuum plate **20**.

### **Integrated Object Holder Systems**

[00061] The invention also provides object holders that integrate two or more of the devices described herein for positioning and retaining objects on a support. For example, the invention provides object holders that utilize pushers and alignment members to precisely position an object, and a vacuum plate as a retaining device to hold the object in the desired position. These integrated object holders typically have an control system that coordinates the actions of the different components of the object holder.

[00062] Figure 7 shows one example of a control system **100** for object holder **10**. Control system **100** generally comprises a controller **105** connected to a plate holder **120** through a plate holder control line **215**. The plate holder control line **215** may terminate in a

connector **210** to facilitate connection to a mating control connector **75** on the plate holder **120**. This arrangement facilitates connection and disconnection of the components. The controller **105** may also be connected to other system components in a high throughput test system through system connection line **285**. For example, the controller **105** matrices instructions from a central control system and report status information in return.

[00063] The controller **105** in this embodiment also controls a vacuum source **115** through vacuum source control line **225** and optionally controls an air supply **110** via air supply control line **220**. In such a manner, the controller can accept instructions or send status information to a high throughput test system controller and control and monitor the precise positioning of a microtiter plate.

[00064] In some embodiments, both the x-axis pusher **50** and the y-axis pusher **35** are activated by air pistons. The air supply **110** provides pressurized air through air supply line **125** which is directed into a y-axis air supply line **130** and an x-axis air supply line **135**. The y-axis air supply line **130** is received into a y-axis air switch **140** which acts as a valve to open or close the y-axis supply line **130**. The y-axis air switch is directed by the controller **105** through x-axis air switch control line **185**. When the controller **105** directs the y-axis air switch **140** to an open position, air pressure is received into the y-axis piston air supply line **150**. The y-axis piston air supply line **150** is connected to the y-axis air piston **160**, which drives a y-axis arm **170**. It will be appreciated that other mechanisms may be used to activate the pushers, such as hydraulic rams, electromagnetic actuators, or gear drives, for example.

[00065] The y-axis arm **170** drives a lever **172** around a pivot **174**. Accordingly, when the air piston **160** is activated, the y-axis pusher pin **35** is moved from its at-rest position. The at-rest position is defined by the spring **176** which attaches between the lever **172** and a spring support **178**. In such a manner the spring **176** causes the lever **172** to pivot from pivot point **174**. In a preferred embodiment of the object holder **10**, when the air piston **160** is not active, the spring causes the y-axis pusher **35** to be firmly engaged against the microtiter plate. Thereby when the air piston **160** is activated, the y-axis pusher **35** is moved away from a wall of the microtiter plate.

[00066] The air piston **160** has a y-axis magnet switch **200** that communicates y-axis arm position **170** to the controller **105** via magnetic switch control line **195**. In such a manner the controller receives a signal indicating the status of the position of the y-axis arm **170**. For example, a signal may be placed on line **195** when the air piston **160** has moved the

y-axis arm **170** in a position that fully disengages the y-axis pusher **35** from the microtiter plate.

[00067] The X-axis air switch **145** is connected to controller **105** through x-axis air switch control line **180**. When the controller **105** directs the x-axis air switch **145** to activate, air pressure is placed in x-axis piston air supply line **155**. Such air pressure drives the x-axis arm **175** of the x-axis air piston **165**. X-axis magnetic switch **205** communicates to controller **105** through magnetic switch control line **190** to generate a signal that indicates the position of x-axis arm **175**. In a preferred example, the x-axis air piston **165** is configured to retract the x-axis pusher **50** when the air piston **165** is deactivated and to force the x-axis pusher **50** against the microtiter plate when the x-axis air piston **165** is activated. When the x-axis air piston **165** is activated and the x-axis pusher **50** is driven firmly against the microtiter plate, the magnetic switch **205** may generate a signal on line **190** which indicates to the controller **105** that the microtiter plate **82** is firmly positioned in the x-axis.

[00068] Referring now to FIGs. 8, 9, and 10, the operation of one embodiment of the y-axis pusher is detailed. The y-axis pusher **35** in this embodiment is a generally L-shaped member having a vertical portion **173** and a horizontal portion **175**. A contact connector **186** is positioned at the top end of the vertical portion **173** for attaching the plate contact **45**. The horizontal portion **175** extends at a right angle from the vertical portion **173** and ends with an enlarged arm contact **182**. The arm contact **182** is constructed and arranged to cooperate with the y-axis arm **170** of the y-axis piston **160**. In a presently preferred arrangement the y-axis arm **170** terminates with an adjustment mechanism for adjusting the length of the y-axis arm.

[00069] The horizontal portion **175** of the lever **172** has a pivot **174** for receiving a pivot pin that enables the y-axis pusher **35** to pivot about the pivot point **174**. The horizontal portion **175** also has a spring connector **184** for receiving one end of the spring **176**. The other end of spring **176** is connected to a stable support such as stable support **178**. In a preferred configuration the spring support **178** is attached to the y-axis air piston and the fixture. When the spring **176** is connected between the spring contact **184** and the stable support **178**, the spring acts to draw the arm contact **182** towards the air piston **160**. As in the illustrated example the lever **172** is configured to pivot about pivot point **174**, the plate contact **45** is rotated in a direction generally away from the air piston.

[00070] In the illustrated embodiment, when the air piston **160** is not activated, the spring **176** acts to press the plate contact **45** toward the y-axis wall **187** of the vacuum

plate 20. If a microtiter plate (not shown in Figs. 8, 9 or 10) is generally positioned on the vacuum plate 20, the plate contact 45 contacts a y-axis wall of the microtiter plate and pushes the plate toward the y-axis protrusions 30. For optimum positioning performance, the y-axis pusher 35 should provide a constant and stable positioning force to the y-axis wall of a microtiter plate. To assure a constant pressure, the force exerted by the y-axis pusher 35 is determined by the spring 176. As springs inherently provide a constant and deterministic force, the microtiter plate will be positioned with a known and constant tensioning force.

[00071] In the preferred embodiment, after the microtiter plate is positioned to the y-axis, the y-axis pusher continues to exert a force against the y-axis wall of the microtiter plate. When the x-axis pusher is activated, the x-axis pusher 50 moves the microtiter plate towards the x-axis protrusion 25. Accordingly, the microtiter plate is moved relative the plate contact 45 and the lever 172 while the y-axis pusher continues to exert a force against the microtiter plate. In that regard the lever 172 must maintain stability in the x-axis direction to avoid skewing and maintain a constant and stable y-axis force. To achieve such stability for lever 172, lever 172 is constructed as a pivoting lever which pivots about pivot point 174. Since the pivot point 174 and the plate contact 45 are generally aligned with the x-axis of the microtiter plate, the pivot acts to substantially stabilize the x-axis positioning of the plate contact 45. Accordingly, when the y-axis pusher 35 is fully tensioned the microtiter plate, and the x-axis pusher moves the microtiter plate towards the x-axis protrusions 25, the y-axis pusher 35 maintains a constant and stable y-axis force. Skewing is also avoided by constructing the plate contact 45 to have a low-friction contact point with the microtiter plate.

[00072] Although in the preferred embodiment, the y-axis pusher is configured as a pivoting lever, it will be appreciated that other configurations may be used to move a microtiter plate towards y-axis protrusions. For example, the plate contact 45 could be directly attached to an air piston arm with the air piston being driven by a constant and stable air force to move the plate contact stably and constantly toward the microtiter plate wall.

[00073] Once the vacuum source has securely retained the microtiter plate against the vacuum plate 20, additional processes may be performed reliably and accurately to the microtiter plate. When processing of the microtiter plate is completed, the vacuum source is deactivated, thereby releasing the microtiter plate from the vacuum plate 20. Subsequently, the x-axis pusher 50 is released and the y-axis pusher 35 is released. With the

vacuum off and the pushers released, the microtiter plate can be easily lifted from the object holder 10 for further processing.

[00074] Referring now to FIG. 11, one example of a preferred arrangement of parts is shown for an object holder 10. FIG. 11 generally shows a bottom side of the fixture 15 with the vacuum plate 20 positioned on the top surface of the fixture 15. Although from the bottom view in FIG. 11 the vacuum plate is not visible, dotted line 21 shows the general positioning of the vacuum plate 20 on the other side of the fixture 15.

[00075] An air source (not shown) is connected to the air supply 125 which runs generally on the perimeter of the fixture to the y-axis air supply line 130 and the x-axis air supply line 135. The y-axis air supply line 130 connects to the y-axis air switch 140 and the x-axis air supply line 135 connects to the x-axis air switch 145. The air switches 140 and 145 electrically connect via electrical lines 185 and 180 to electrical connector 75, and then connect to the controller 105 through connector 210 and control line 215. Accordingly, the controller can then direct the air switches to activate or deactivate the air pistons. For example, the controller can direct y-axis air switch 140 to activate, thereby pressurizing y-axis air supply line 150 and driving the arm 170 of air piston 160. When the arm 170 is driven, the lever 172 pivots about pivot point 174 and pulls the y-axis pusher lever away from the vacuum plate. When the controller deactivates the y-axis air switch 140, air bleeds from the piston 160 and the spring 176, which is under tension between spring contact 184 and stable support 178, tensions the y-axis pusher towards the vacuum plate. Magnetic switch 200 communicates to the controller 105 through control line 190 for indicating y-axis pusher position.

[00076] The controller also controls x-axis air switch 145, which when opened pressurizes x-axis piston air supply line 155 for driving the x-axis arm 175 of x-axis air piston 165. Accordingly, the x-axis pusher 50 is propelled toward the vacuum plate 20. In a preferred embodiment, the x-axis pusher is directly attached to the x-axis arm 175. It will be appreciated that other configurations and arrangements may be used for attaching the x-axis pusher to the x-axis arm. To conserve space, the x-axis piston is arranged so that the arm 175 is pulled into the piston body 165 when air pressure is applied to the piston 165. When pressure is released, the arm 175 travels in a manner so that the x-axis pusher 50 is released from any retained microtiter plate. Magnetic switch 205 connects to controller 105 via line 195 so that the controller 105 can receive a signal that the x-axis pusher 50 is fully engaged against the microtiter plate.

[00077] Referring now to FIG. 12, a method of retaining a microtiter plate 300 is shown. In block 305, the microtiter plate is generally positioned relative to x and y locating protrusions. To facilitate ease of general positioning, both the x-axis and the y-axis pushers are positioned away from the microtiter plate. In the preferred embodiment, the y axis air piston is active and the x axis piston not active to position the protrusions away from the plate. It will be appreciated that other arrangements may be substituted.

[00078] The plate can be generally positioned using any conventional means, including robotic positioning. Although such general robotic positioning may be sufficient to place the plate adjacent the protrusions, such general positioning is not sufficiently accurate for high throughput automated use. Once the plate is generally positioned, the object holder may receive a signal that the plate is generally positioned and ready to be precisely positioned in a desired orientation.

[00079] Block 310 shows that the y-axis pusher is positioned in tension against a y-axis wall of the microtiter plate. In a preferred arrangement, the y-axis pusher is released to an at-rest position where a spring provides a constant and determined tension between the y-axis pusher and the microtiter plate. When the y-axis pusher is released, the y-axis pusher comes into tensioned contact with a y-axis wall of the microtiter plate. As the y-axis pusher is tensioned against the y-axis wall of the microtiter plate, the microtiter plate is pushed firmly against the y-axis protrusions. As a short period of time may be required to constantly tension and move the microtiter plate, the system waits for the system to settle in block 315.

[00080] The y-axis pusher may have an indication of when the y-axis pusher is in a particular position. If such an indicator is used, the indicator may be, for example, a switch which closes when the y-axis pusher is in position. In a preferred embodiment, the switch is a magnetic switch coupled to an air piston moving the y-axis pusher. It will be appreciated that other sensors or indicators may be substituted. Accordingly, block 320 checks to see if the switch is closed, and if the switch is closed, the x-axis pusher is activated in block 325. If the switch does not close in the allotted time, the system is notified that the microtiter plate is not positionable in block 355, and the process would typically be aborted.

[00081] With the x-axis pusher activated in block 325, the x-axis pusher is moved toward the microtiter plate, thereby positioning the microtiter plate firmly against the x-axis protrusion. As moving the microtiter plate in the x-axis direction may take a period of time, the system waits in block 330. As with y-axis pusher, the x-axis pusher may have an indicator of when the x-axis pusher is firmly in position. Accordingly, block 335 checks to



see if this indicator switch is closed, and if it is closed, the vacuum source is activated in block 340. However, if the switch does not close, the system is notified that the plate is not positionable in block 355.

[00082] In block 340, the vacuum source is activated, causing the vacuum lines to withdraw air from the vacuum plate area. The vacuum source will preferably cause the bottom surface of the microtiter plate to be drawn to the vacuum plate in a secure manner. The vacuum plate may have a vacuum switch for determining when sufficient vacuum has been created to securely retain the microtiter plate. If the vacuum switch is not closed, then block 345 directs the system to be notified that the plate is not properly positioned. However, if the vacuum switch does close, this is a positive indication that the microtiter plate is firmly and precisely positioned, and therefore the system is notified in block 350 that the plate is ready for further processing.

[00083] Referring now to FIG. 13, one embodiment of a method of releasing a microtiter plate is described, which is essentially the reverse process of that described in the method of retaining the plate 300. Block 405 shows that the microtiter plate has finished processing and the system is notified that the microtiter plate can now be removed. In block 410, the vacuum source is deactivated, which should open the vacuum switch 275 shown in FIG. 11. If the switch does open, then the x-axis pusher is deactivated in block 420, and after a period of time, the switch is checked in block 430 to verify that the x-axis pusher has moved. If the x-axis pusher has moved, then the y-axis pusher is activated to move the y-axis pusher away from the microtiter plate. After a period of time, the switch should open thereby indicating the y-axis pusher is moved away from the microtiter plate. If the switch does properly open, then the system is notified that they plate is ready to be moved. Accordingly, another robotic system can be used to grip the plate and move the plate to a next station for processing. If any of the switches do not indicate properly, then the system is notified that the plate is not moveable in block 455. In that regard, manual intervention will probably be used to remove the plate.

[00084] The invention also provides algorithms and computer software for programming a controller to automatically carry out the described object positioning and/or retention procedures described herein. Also provided are computers that are programmed to carry out one or more of the positioning and retention procedures.

[00085] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof



will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2
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25